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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,158	10/25/2001	Masayoshi Nanba	46342/56603	8650

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David G Conlin
Dike Bronstein Robert & Cushman
130 Water Street
Boston, MA 02109

EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/05/2002

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,158	NANBA ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *5-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of Invention I, Claims 1-4 and species CYP3A4 in Paper No. 12 is acknowledged. Claims 5-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim.

Specification

The disclosure is objected to because of the following informalities:

Abstract

The abstract of the disclosure is objected to because of poor grammar; for example, "This invention relates to cell lines that obtained using cultured cell lines as a host and stably express a number of human cytochromes P450" lacks clarity. In addition, the second paragraph is a single run-on sentence. The abstract should comprise a single paragraph, not two paragraphs. Correction is required. See MPEP § 608.01(b).

Tables

Table I appears twice in the specification. It is included with the figures as well as within Example 3 of the specification. In addition, the sheet included with the figures is not labeled. It is requested that the sheet of Table I included with the figures be removed.

Grammar

35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with sentence construction that is not clear, concise and exact. The specification should be revised carefully in order to comply with

35 U.S.C. 112, first paragraph. Examples of some unclear, inexact or verbose sentences used in the specification are:

Page 3 line 31-34 "Also, these enzymes....test system." is unclear.

Page 8 line 18-25 "In view of ... endogenous substrates." is a run-on sentence.

These two examples are not meant to comprise all problems; the applicants are required to check the specification carefully and make appropriate corrections.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In Claim 1, the phrase "...capable of stably expressing..." renders the claim indefinate as, it is not clear whether the cell line does or does not express CYP1A1 etc. Claims 2-4, which are dependent on Claim 1, are rejected for the same reason.

In Claims 1 and 2, for the phrase "... stably expressing...", it is unclear whether the cytochrome P450 is endogenous to the cell line or is introduced by transfection. Claims 2-4, which are dependent on Claim 1, are rejected for the same reason.

For Claim 2, the interpretation of the phrase "...wherein human cytochromes P450 are capable of stably expressing CYP1A1..." is that the cytochromes P450 are expressing CYP1A1 etc. This is not correct; it is the isolated cell line that is expressing CYP1A1 etc.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for the Hepc/1A1.4, Hepc/1A2.9, Hepc/2A6L.9, Hepc/2B6.68, Hepc/2C8.46, Hepc/2C9.1, Hepc/2C19.12, Hepc/2D6.39, Hepc/2E1.3-8, and Hepc/3A4.5 cell lines. However, the specification does not reasonably provide enablement for any human hepatic carcinoma cell line stably expressing any human cytochrome P450 or any human hepatic carcinoma cell line stably expressing CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is so broad as to encompass any human hepatic carcinoma cell line expressing any human cytochrome P450. Claim 2 is so broad as to encompass any human hepatic carcinoma cell line expressing CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of cell lines broadly encompassed by the claims. Since the complement of protein expressed by a cell determines its structural and functional properties, predictability of which proteins can be changed in a cell and obtain the desired utility of expressing any human cytochrome P450, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1,

requires a knowledge of and guidance with regard to which proteins are necessary, unnecessary, or inhibitory for the recited utility and a detailed knowledge of the ways in which each cellular protein's function relates to the function of the hepatic cell line. However, in this case the disclosure is limited to the Hepc/1A1.4, Hepc/1A2.9, Hepc/2A6L.9, Hepc/2B6.68, Hepc/2C8.46, Hepc/2C9.1, Hepc/2C19.12, Hepc/2D6.39, Hepc/2E1.3-8, and Hepc/3A4.5 cell lines.

While recombinant and screening techniques are known, it is not routine in the art to screen for alterations in multiple cellular proteins and/or multiple cell lines, as encompassed by the instant claims. Furthermore, which proteins can be altered with a reasonable expectation of success in obtaining the desired activity/utility are limited in any cell and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to alteration in expression of a single protein to diminish with each further protein altered e.g. multiple protein alterations in a single cell line.

The specification does not support the broad scope of Claims 1 and 2 which, encompasses all cell lines derived from human hepatic carcinoma that stably express any human cytochrome P450 or stably express CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP2E1. The specification does not support the broad scope of Claims 1 and 2 because the specification does not establish: (A) which proteins may be modified without effecting the ability of the hepatic cell line to stably express any cytochrome P450; (B) the general tolerance, for stable expression of any cytochrome P450 in any hepatic cell line, to modification of cellular proteins and extent of such tolerance; (C) a rational and predictable scheme for selecting hepatic cell line with modified proteins with an expectation of obtaining the desired stable expression of any cytochrome P450; and (D) the specification provides insufficient

guidance as to which of the essentially infinite possible choices of hepatic cell lines with essentially infinite variations in their complement of proteins is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of hepatic cell lines, with essentially infinite variations in their complement of proteins, that are able to stably express any cytochrome P450. Without sufficient guidance, determination of the identity of cells having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of human hepatic cell lines, with essentially infinite variations in their complement of proteins, which are able to stably express any cytochrome P450. The specification teaches the structure of only 14 representative species of such cell lines which, are all derived from a single parental hepatic cell line, HepG2. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a human hepatic cell lines that is able to stably express any cytochrome P450 including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Given this lack of description of representative

species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Dai et al, 1993 (in IDS). Dai et al teach the stable expression of human P4502E1 in HepG2 cells (for example, Fig 2). Since, Claim 1 recites a cell line derived from human hepatic carcinoma capable of stably expressing a human P450, Claim 2 recites expression of CYP2E1, and Claim 3 recites HepG2 cells, Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Dai et al, 1993.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dai et al, 1993 in view of GenBank Acc# J04449, 1994 and further in view of Waxman et al, 1991. The teachings of Dai et al are described above. Dai et al do not teach stable expression of CYP3A4 in HepG2 cells. GenBank Acc# J04449 teaches the sequence of CYP3A4 (see pg 34, line 30 of

the specification). It would have been obvious to a person of ordinary skill in the art to use the sequence of GenBank Acc# J04449 to prepare HepG2 cells stably expressing CYP3A4. Stably expressing CYP3A4 in HepG2 cells is suggested by Waxman et al who teach expression of CYP3A5 in Hepc cells using vaccinia virus (Table 1) which is more difficult than using the plasmid-mediated methods of Dai et al. Motivation to use the sequence of GenBank Acc# J04449 to prepare HepG2 cells stably expressing CYP3A4 is provided by the desire to characterize the CYP3A4 enzyme in a stable, reproducible hepatic cell system. The expectation of success is high since HepG2 cells stably expressing another form P450 have been established (Dai et al, 1993). Therefore, Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dai et al, 1993 in view of GenBank Acc# J04449, 1994 and further in view of Waxman et al, 1991.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 8:30-5 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600